IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the application of: Vincent Dubois. et al.	Group Art Unit: 1654
Serial No.: 09/879,442	Examiner: Andrew D. Kosar
Filed: June 11, 2001	
For: Enzyme Cleavable Prodrug Compounds	
Attorney Docket No.: MXI-321CPRCE	

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF SANJEEV GANGWAR, PH.D. UNDER 37 CFR §1.132

Dear Sir:

I, Sanjeev Gangwar, Ph.D., a citizen of United States, residing in Foster City, California, hereby declare as follows:

1. I am presently a Sr. Director of Medicinal Chemistry at Medarex, Inc. I have been working in the area of tumor selective prodrugs and pharmaceuticals for approximately 15 years. A copy of my curriculum vitae is attached as Appendix A.

2. I am a co-inventor of the above referenced patent application, along with Vincent Dubois, Ann-Marie Fernandez, Evan Lewis, Thomas J. Lobl, Matthew H. Nieder, Lesley B. Pickford, Andre Trouet, and Geoffrey Yarranton.

3. I have read the above-referenced application (included herewith as Appendix B) and pending claims 2-3, 5-21, 26-30, 37, 118-120, and 122-134 (included herewith as Appendix C). It is my understanding that the claimed invention is directed to compounds comprising: (1) a therapeutic agent capable of entering a target cell, (2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein AA^4 is an amino acid not encoded by mammals, (3) a negatively charged stabilizing group, and (4) optionally, a linker group not cleavable by TOP. I understand that the claims are further directed to pharmaceutical compositions containing such compounds.

4. In addition, I understand that claims 2, 3, 5-8, 11, 13-19, 23-26, 28-30, 37, 118, 119, 120 and 122-125 have been rejected under 35 U.S.C. § 103 (a) as being unpatentable over Trouet *et al.* (WO 96/05863) or Trouet *et al.* (U.S. Patent No. 5,962,216) (collectively hereinafter referred to as "Trouet *et al.*"), each in view of Li *et al.* (*J. Biol. Chem.* (1990) 235, 2638-2641), Holcenberg *et al.* (*J. Biol. Chem.* (1975), 250 (11) 4165-4170), Hall (U.S. 4,144,333), Guthiel (U.S. 5,574,107), or LaRochelle (U.S. 5,833,986), as set forth at pages 4-6 of the Office Action dated January 17, 2007. In particular, the Examiner asserts that succinylation of the positively charged prodrug, βAla-Leu-Ala-Leu-Dox, taught by Trouet *et al.*, would have been obvious in view of the secondary references which teach succinylation for the purposes of (1) increasing the half life of proteins (Li *et al.* and Holcenberg *et al.*) and (2) protecting amino groups from degradation (Gutheil and Hall).

5. It is my opinion that the foregoing references would not have made the presently claimed invention obvious, because the reasons for succinylating proteins taught by these references would not have applied to the prodrug peptides recited in the present claims, including βAla-Leu-Ala-Leu-Dox.

Specifically, one of ordinary skill in the art would not have been motivated to succinylate the βAla-Leu-Ala-Leu-Dox prodrug described by Trouet *et al.* to increase the prodrug's half-life and/or protect it from degradation, because Trouet *et al.* explicitly teach that the prodrugs "remain stable in the serum and in the blood, and [are] insensitive to the action of the circulating proteinases and peptidases associated with the red cells" (see e.g., U.S.5,962,216, col. 8, lines 41-44).

In fact, Trouet *et al.* teach that the use of a non-genetically encoded amino acid (i.e., an amino acid not present in mammals), such as β-alanine, alone is sufficient to stabilize such prodrugs and to prevent their degradation *in vivo.* Trouet *et al.* also teach that succinyl groups alone can be used as stabilizing groups. The authors do not teach or suggest the use of succinyl groups in combination with at least one non-genetically encoded amino acid, as presently claimed, for any purpose.

Similarly, although Holcenberg *et al.*, Li *et al.*, Gutheil, and Hall teach the use of succinylation to decrease the amount of degradation of proteins *in vivo,* one of ordinary skill in the art would not have been motivated to apply this use to the prodrugs recited in the present claims, because Trouet *et al.* taught that these prodrugs were already

specifically designed to be stable in whole blood and selectively cleaved in the vicinity of particular target cells.

For at least the foregoing reasons, it is my opinion that the use of negatively charged stabilizing groups, such as succinyl, in the prodrugs of the presently claimed invention would not have been obvious over the prior art.

6. I also understand that the Examiner has questioned whether the use of negatively charged stabilizing groups, other than succinyl, together with positively charged prodrugs, other that βAla-Leu-Ala-Leu-Dox, would have the same unexpected property of reduced toxicity as Succ-βAla-Leu-Ala-Leu-Dox. In this regard, the Examiner questions whether the reduction in toxicity could have been due to an increase in half-life of the prodrug, rather than a decrease in its positive charge.

7. It is my opinion that other positively charged prodrugs, such as those described in the present application would exhibit the same acute toxicity as does the βAla-Leu-Ala-Leu-Dox prodrug tested in the present application (i.e., that other positively charged prodrugs would, like βAla-Leu-Ala-Leu-Dox, form toxic aggregates when administered *in vivo*). It is also my opinion that the toxicity of these prodrugs would, like βAla-Leu-Ala-Leu-Dox, be decreased upon the addition of a negatively charged stabilizing group. It is also my opinion that both succinyl and other negatively charged stabilizing groups would similarly mask the positive charge of the peptide and prevent the formation of the toxic aggregates. Indeed, experiments that I have performed have shown that the reduction in toxicity is directly related to the masking of the positive charge. For example, co-administration with heparin reduced toxicity, without substantially modifying the prodrugs' half-life.

8. I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under §1001 of Title XVIII of the United States Code, and that such willful false statements may jeopardize the validity of this Application for Patent or any patent issuing thereon.

Sanjeev Gangwar — June 18th, 07

Sanjeev Gangwar, Ph.D. — Date

Appendix A

SANJEEV GANGWAR, Ph.D.
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Foster City, CA 94034
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SUMMARY:

- Held positions of increasing responsibility in pharmaceutical R & D
- Demonstrated success in management of drug discovery and development programs in several companies
- Moved drug candidates in the area of cancer from their discovery to preclinical development
- Extensive multi-step industry synthesis experience for various biologically active compounds such as complex heterocycles, polyamides, carbohydrates, natural products and peptidomimetics
- Extensive background in enzyme-sensitive prodrug strategies including site-specific, chemotherapeutic prodrugs and antibody-drug conjugates
- Managed the cGMP scale up of clinical compounds through contract manufacturing labs, including optimization of key steps
- Member of the management team driving corporate strategy, strategic planning and project implementation
- Involved in partnering efforts, developed international collaborations, and established and managed assorted vendors

EXPERIENCE:

4/02- present **Medarex, Inc.** Sunnyvale, CA
Sr. Director, Medicinal Chemistry

- Directed teams to develop novel minor groove binder conjugates resulting in several composition of matter patents
- Designed and synthesized novel cancer therapeutic molecules resulting in favorable pharmacokinetics and relatively low toxicities
- Designed a series of focused libraries on the basis of SAR resulting in a lead candidate for further development
- Managed the design, synthesis and development of several antibody-drug conjugates, which are currently in preclinical development.
- Conceived and developed a new process for the synthesis of a drug candidate which is currently in preclinical development
- Worked closely with project teams of cell biologists, biochemists and pharmacologists to identify and develop clinical candidates

- Outsourced and managed contract manufacturing at several sites for several drug substances
- Responsible for presentation of chemistry strategy and progress in company meetings
- Successfully managed and supervised a team of 5 Ph.D scientists and 3 research associates.

6/98- 4/2002 **Corixa Corporation** (Formerly Coulter Pharmaceutical) S. San Francisco, CA
Sr. Scientist/Group Leader, Medicinal /Process Chemistry

- Developed and synthesized several tumor activated prodrugs of anthracyclines. This work has led to the filing of several patents.
- Managed the design, synthesis and development of CPI-0004, which is currently in clinical development.
- Synthesized high-affinity ligands based on the structure-activity relationship and devised the best route for the synthesis of a novel class of compounds that are being used in targeting HER2 positive breast tumors.
- Successfully devised and synthesized an integrin-targeted doxorubicin prodrug for the treatment of tumors.
- Synthesized several analogs of RC-529, a complex carbohydrate derivative that has been shown in preclinical experiments to enhance the specific immune response to the vaccine antigen.
- Conceived and developed a new process for the synthesis of CPI-0004 which is currently in clinical development.
- Improved and simplified an existing synthetic process for CPI-0004 by eliminating chromatography steps and coordinated efforts with API manufacturer to design innovative synthetic solutions towards developing new routes.
- Served on Transitional Project Review Committee (T-PRC) to review development projects in terms of project viability and resources and make appropriate recommendations to Corixa senior management team.
- Participated in strategic partnering activity to select a corporate partner for the company's proprietary technology platform.
- Successfully managed and supervised research associates.

1996- 98 **Prolinx, Inc.**, Bothell, Washington
Research Scientist, Medicinal Chemistry

- Designed and synthesized small peptidomimetic and phenylboronic acid libraries using solid-phase approach.
- Improved and scaled up syntheses of pyrrole and imidazole amino acids that are better able to recognize and bind tightly to specific double-stranded DNA sequences.

- Synthesized high-affinity ligands based on structure-activity relationship and devised the best route for the synthesis of a novel class of complexing compounds that are used in the detection of gene probes and in gene therapy.
- Successfully devised and synthesized several analogs of Octreotide to deliver radioactivity to target tissues.

1993-96 **University of Kansas,** Pharmaceutical/Medicinal Chemistry Dept, Lawrence, KS
Postdoctoral Research Associate. Advisor: Professor Ronald T. Borchardt

- Patented two highly efficient prodrug strategies (15-step syntheses) that significantly enhance the metabolic stability and the intestinal permeability of a model opioid peptide
- Synthesized several prodrugs using solid- and solution-phase chemistry and determined their chemical and enzymatic stabilities using HPLC
- Determined solution conformation of the prodrugs using 2-D NMR, circular dichroism and molecular dynamics simulations and explored the role of solution conformation in determining membrane permeability

1986-92 **University of Arizona,** Department of Chemistry, Tucson, Arizona
Research Assistant. Advisor: Professor Robert B. Bates

- Devised and completed a 36-step synthesis of a stereoisomer of Dolastatin-11, a potent marine macrocyclic anti-tumor agent that is presently in clinical development
- Prepared synthons for the unusual amino acids found in Dolastatin-11
- Developed asymmetric synthesis for the β-amino acid unit and established the absolute stereochemistry of two chiral centers in Dolastatin-11
- Synthesized twenty-two new tripeptide-like analogs of peptidoglycan for testing as possible β-lactamase inhibitors

1982-85 **University of Delhi,** Department of Chemistry, Delhi, India
Unilever Research Assistant. Advisor: Professor G.B.V. Subramanian.

- Synthesized several analogs of aleuritic acid as potential insect sex pheromones.

EDUCATION:

1992 Ph.D., Organic Chemistry
University of Arizona, Tucson.

1989 M.S., Organic Chemistry
University of Arizona, Tucson.

1982 B.S., Chemistry
St. John's College, Agra, India

Continuing Education:

- Organic chemistry of drug design and drug action by ACS, New Orleans, LA 8/99.
- Bioconjugate chemistry by ACS, San Francisco, CA 3/00.

HONORS AND AWARDS:

- Unilever U.K., Research Foundation Award recipient at the University of Delhi (1982-1985).
- Glaxo Inc., Postdoctoral Fellowship recipient at the University of Kansas (1993-95).

PATENTS: 14 (see Addendum)

PUBLICATIONS: 26 (see Addendum)

PRESENTATIONS: 16 (see Addendum)

REFERENCES: Available upon request.

ADDENDUM

PATENTS:

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L.B. Pickford, **S. Gangwar**, T.J. Lobl, M.H. Nieder, G.T. Yarranton, Prodrug compounds with isoleucine. PCT Int. Appl. **2001**, 107 pp.

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C. Bebbington, M. Nieder , P. Cardarelli, **S. Gangwar**, L. Pickford. CD-10 activating, filed on June 11, **2001,** US serial NO. 037877-2126.

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A. Bak, S.O. Gudmundsson, **S. Gangwar,** T.J. Siahaan, R.T. Borchardt. Acyloxyalkoxy cyclic prodrugs of opioid peptides, 12th Annual Meeting of the American Association of Pharmaceutical Scientists, Boston, Massachusetts, November 2-4, **1997**.

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G.M. Pauletti, **S. Gangwar,** B. Wang, T.J. Siahaan, D.G. Vander Velde, R.T. Borchardt. Novel prodrug approaches to prepare cyclic peptides with enhanced membrane permeability and enzymatic stability. II. 3-(2'-hydroxy-4',6'-dimethylphenyl)-2,2-dimethyl propionic acid pro-moiety, 10th Annual Meeting of the American Association of Pharmaceutical Scientists, Miami Beach, Florida, November 5-9, **1995.**

APPENDIX C:
PENDING CLAIMS

2. The compound of claim 5 wherein n is an integer from 0 to 8.

3. The compound of claim 5 wherein the target cell is a tumor or inflammatory cell.

5. A compound comprising:

(1) a therapeutic agent capable of entering a target cell,

(2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein:

each AA independently represents an amino acid,

n is an integer from 0 to 16,

AA^4 represents β-alanine, thiazolidine-4-carboxylic acid, 2-thienylalanine, 2-naphthylalanine, D-alanine, D-leucine, D-methionine, D-phenylalanine, 3-amino-3-phenylpropionic acid, γ-aminobutyric acid, 3-amino-4,4-diphenylbutyric acid, tetrahydroisoquinoline-3-carboxylic acid, 4-aminomethylbenzoic acid, and aminoisobutyric acid,

AA^3 represents any amino acid,

AA^2 represents any amino acid, and

AA^1 represents any amino acid,

(3) a negatively charged stabilizing group, and

(4) optionally, a linker group not cleavable by TOP,

wherein the oligopeptide is directly linked to the stabilizing group at the amino terminus of the oligopeptide and the oligopeptide is directly linked to the therapeutic agent or indirectly linked through the linker group to the therapeutic agent at a second attachment site of the oligopeptide,

wherein the stabilizing group reduces acute toxicity of the compound when administered *in vivo*, and

wherein the compound is cleavable by TOP.

6. The compound of claim 5 wherein TOP is present in the extracellular vicinity of the target cell for the therapeutic agent.

7. The compound of claim 5 wherein TOP cleaves the linkage between AA^3 and AA^2 of the oligopeptide.

8. The compound of claim 5 being a prodrug having an active portion, wherein the active portion of the prodrug is more capable of entering the target cell after cleavage by TOP than prior to cleavage by TOP, the active portion including at least the therapeutic agent.

9. The compound of claim 8 wherein the active portion of the prodrug consists of the therapeutic agent.

10. The compound of claim 8 wherein the active portion of the prodrug includes the therapeutic agent and at least the linker group.

11. The compound of claim 8 wherein the active portion of the prodrug includes the therapeutic agent and AA^1 of the oligopeptide.

12. The compound of claim 11 wherein the active portion of the prodrug further comprises AA^2 of the oligopeptide linked to AA^1.

13. The compound of claim 5 wherein the oligopeptide is selected from the group consisting of: D-AlaThiβAlaβAlaLeuAlaLeu (SEQ ID NO: 1), ThiβAlaβAlaLeuAlaLeu (SEQ ID NO: 2), βAlaβAlaLeuAlaLeu (SEQ ID NO: 3), βAlaLeuTyrLeu (SEQ ID NO: 17), βAlaLeuThiLeu (SEQ ID NO: 18), βAlaLeuThrLeu (SEQ ID NO: 21), βAlaLeuSerLeu (SEQ ID NO: 22), βAlaLeuPyrLeu (SEQ ID NO: 23), βAlaLeuLeuLeu (SEQ ID NO: 24), βAlaLeuGlyLeu (SEQ ID NO: 28), βAlaLeuPheLeu (SEQ ID NO: 31), βAlaLeuAibLeu (SEQ ID NO: 32), and βAlaLeuAlaLeu (SEQ ID NO: 38).

14. The compound of claim 5 wherein AA^1 of the oligopeptide is selected from the group consisting of Leucine, Phenylalanine, Isoleucine, Alanine, Glycine, Tyrosine, 2-Naphthylalanine, Serine, p-Cl-phenylalanine, p-Nitrophenylalanine, 1-Naphthylalanine, Threonine, Homoserine, Cyclohexylalanine, Thienylalanine, Homophenylalanine, Norleucine, and β-Alanine.

15. The compound of claim 5 wherein AA^2 of the oligopeptide is selected from the group consisting of Alanine, Leucine, Tyrosine, Glycine, Serine, 3-Pyridylalanine, 2-Thienylalanine, Norleucine, Homoserine, Homophenylalanine, p-Cl-phenylalanine, p-Nitrophenylalanine, Aminoisobutyric Acid, Threonine, and Phenylalanine.

16. The compound of claim 5 wherein AA^3 of the oligopeptide is selected from the group consisting of Leucine, Tyrosine, Phenylalanine, p-Cl-Phenylalanine, p-Nitrophenylalanine, Valine, Norleucine, Norvaline, Phenylglycine, Tryptophan, Tetrahydroisoquinoline-3-carboxylic acid, 3-Pyridylalanine, Alanine, Glycine, Thienylalanine, Methionine, Valine, and Proline.

17. The compound of claim 125 wherein AA^4 is selected from the group consisting of β-Alanine, Thiazolidine-4-carboxylic acid, 2-Thienylalanine, 2-Naphthylalanine, D-Alanine, D-Leucine, D-Methionine, D-Phenylalanine, 3-Amino-3-phenylpropionic acid, γ-Aminobutyric acid, 3-Amino-4,4-diphenylbutyric acid, Tetrahydroisoquinoline-3-carboxylic acid, 4-Aminomethylbenzoic acid, and Aminoisobutyric acid.

18. The compound of claim 5 wherein the stabilizing group is a dicarboxylic or higher order carboxylic acid.

19. The compound of claim 5 wherein the stabilizing group is selected from the group consisting of: succinic acid, adipic acid, glutaric acid, phthalic acid, diglycolic acid, fumaric acid, naphthalene dicarboxylic acid, 1,8-naphthyl dicarboxylic acid, aconitic acid, carboxycinnamic acid, triazole dicarboxylic acid, butane disulfonic acid, and maleic acid.

20. The compound of claim 5 wherein the stabilizing group is a non-genetically encoded amino acid having four or more carbons.

21. The compound of claim 5 wherein the stabilizing group is one of aspartic acid linked to the oligopeptide at the β-carboxy group of the aspartic acid or glutamic acid linked to the oligopeptide at the γ-carboxy group of the glutamic acid.

23. The compound of claim 5 wherein the stabilizing group is selected to reduce interaction between the compound and endothelial cells that line blood vessels when administered intravenously to the patient.

24. The compound of claim 5 wherein the therapeutic agent is selected from the group consisting of Alkylating Agents, Antiproliferative agents, Tubulin Binding agents, Vinca Alkaloids, Enediynes, Podophyllotoxins or Podophyllotoxin derivatives, the Pteridine family of drugs, Taxanes, Anthracyclines, Dolastatins, Topoiosomerase inhibitors, and Platinum complex chemotherapeutic agents.

25. The compound of claim 5 wherein the therapeutic agent is selected from the group consisting of Doxorubicin, Daunorubicin, Vinblastine, Vincristine, Calicheamicin, Etoposide, Etoposide phosphate, CC-1065, Duocarmycin, KW-2189, Methotrexate, Methopterin, Aminopterin, Dichloromethotrexate, Docetaxel, Paclitaxel, Epithiolone, Combretastatin, Combretastatin A4 Phosphate, Dolastatin 10, Dolastatin 11, Dolastatin 15, Topotecan, Camptothecin, Mitomycin C, Porfiromycin, 5-Fluorouracil, 6-Mercaptopurine, Fludarabine, Tamoxifen, Cytosine arabinoside, Adenosine arabinoside, Colchicine, Cisplatin, Carboplatin, Mitomycin C, Bleomycin, Melphalan, Chloroquine, Cyclosporin A, a derivative of any of the foregoing, and an analog of any of the foregoing.

26. The compound of claim 5 wherein the oligopeptide is directly linked to the therapeutic agent.

27. The compound of claim 5 wherein the oligopeptide sequence is indirectly linked to the therapeutic agent at the second attachment site of the oligopeptide via a linker group, the linker group selected from the group consisting of amino caproic acid, a hydrazide group, an ester group, an ether group, and a sulphydryl group.

28. A compound selected from the group consisting of Suc-βAla-Leu-Ala-Leu-Dox, Suc-βAla-Leu-Ala-Leu-Dnr, and Glutaryl-βAla-Leu-Ala-Leu-Dox.

29. The compound of claim 5 wherein the compound is resistant to cleavage by CD10.

30. A conjugate comprising an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein: each AA independently represents an amino acid, n is an integer from 0 to 16, AA^4 represents a non-genetically-encoded amino acid, AA^3 represents any amino acid, AA^2 represents any amino acid, and AA^1 represents any amino acid, wherein the oligopeptide is cleavable by TOP, the oligopeptide is linked to a therapeutic agent and the oligopeptide is linked to a negatively charged stabilizing group at the amino terminus of the oligopeptide, wherein the stabilizing group reduces acute toxicity of the conjugate when administered *in vivo*, wherein said non-genetically encoded amino acid is selected β-alanine, thiazolidine-4-carboxylic acid, 2-thienylalanine, 2-naphthylalanine, D-alanine, D-leucine, D-methionine, D-phenylalanine, 3-amino-3-phenylpropionic acid, γ-aminobutyric acid, 3-amino-4,4-diphenylbutyric acid, tetrahydroisoquinoline-3-carboxylic acid, 4-aminomethylbenzoic acid, and aminoisobutyric acid.

37. A pharmaceutical composition comprising

(1) a compound comprising:

(a) a therapeutic agent capable of entering a target cell,

(b) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein:

each AA independently represents an amino acid,

n is an integer from 0 to 16,

AA^4 represents β-alanine, thiazolidine-4-carboxylic acid, 2-thienylalanine, 2-naphthylalanine, D-alanine, D-leucine, D-methionine, D-phenylalanine, 3-amino-3-phenylpropionic acid, γ-aminobutyric acid, 3-amino-4,4-diphenylbutyric acid, tetrahydroisoquinoline-3-carboxylic acid, 4-aminomethylbenzoic acid, and aminoisobutyric acid,

AA^3 represents any amino acid,

AA^2 represents any amino acid, and

AA^1 represents any amino acid,

(c) a negatively charged stabilizing group, and

(d) optionally, a linker group not cleavable by TOP,

wherein the oligopeptide is directly linked to the stabilizing group at the amino terminus of the oligopeptide and the oligopeptide is directly linked to the therapeutic agent or indirectly linked through the linker group to the therapeutic agent at a second attachment site of the oligopeptide,

wherein the stabilizing group reduces acute toxicity of the compound when administered *in vivo*, and

wherein the compound is cleavable by TOP,

and (2) a pharmaceutically acceptable carrier.

118. The compound of claim 5 wherein the oligopeptide is βAla-Leu-Ala-Leu (SEQ ID NO: 38).

119. The compound of claim 28 wherein the compound is Suc-βAla-Leu-Ala-Leu-Dox.

120. A pharmaceutical composition comprising the compound of claim 119 and a pharmaceutically acceptable carrier.

122. The compound of claim 5, wherein the stabilizing group also hinders cleavage of the compound by enzymes present in whole blood.

123 The conjugate of claim 30, wherein the stabilizing group also hinders cleavage of the conjugate by enzymes present in whole blood.

124. The pharmaceutical composition of claim 37, wherein the stabilizing group also hinders cleavage of the compound by enzymes present in whole blood.

125. A compound comprising:

(1) a therapeutic agent capable of entering a target cell, wherein said therapeutic agent is an alkylating agent, antiproliferative agent, tubulin binding agent, vinca alkaloid, enediyne, podophyllotoxin, podophyllotoxin derivative, a member of the pteridine family of drugs, taxane, dolastatins, topoiosomerase inhibitor, or a platinum complex chemotherapeutic agent;

(2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein:

each AA independently represents an amino acid,

n is an integer from 0 to 16,

AA^4 represents a non-genetically-encoded amino acid,

AA^3 represents any amino acid,

AA^2 represents any amino acid, and

AA^1 represents any amino acid,

(3) a negatively charged stabilizing group, and

(4) optionally, a linker group not cleavable by TOP,

wherein the oligopeptide is directly linked to the stabilizing group at the amino terminus of the oligopeptide and the oligopeptide is directly linked to the therapeutic agent or indirectly linked through the linker group to the therapeutic agent at a second attachment site of the oligopeptide,

wherein the stabilizing group reduces acute toxicity of the compound when administered *in vivo*, and

wherein the compound is cleavable by TOP.

126. The compound of claim 2 wherein n is 0.

127. The compound of claim 17 wherein the stabilizing group is selected from the group consisting of: succinic acid, adipic acid, and glutaric acid.

128. The conjugate of claim 30 wherein n is 0.

129. The conjugate of claim 30 wherein the stabilizing group is selected from the group consisting of: succinic acid, adipic acid, and glutaric acid.

130. The pharmaceutical composition of claim 37 wherein n is 0.

131. The pharmaceutical composition of claim 37 wherein the stabilizing group is selected from the group consisting of: succinic acid, adipic acid, and glutaric acid.

132. The compound of claim 125 wherein n is 0.

133. The compound of claim 125 wherein the stabilizing group is selected from the group consisting of: succinic acid, adipic acid, and glutaric acid.

134. A compound comprising:

(1) a therapeutic agent capable of entering a target cell,

(2) an oligopeptide of the formula $(AA)_n$-AA^4-AA^3-AA^2-AA^1, wherein:

each AA independently represents an amino acid,

n is 0,

AA^4 represents β-alanine, thiazolidine-4-carboxylic acid, 2-thienylalanine, 2-naphthylalanine, D-alanine, D-leucine, D-methionine, D-phenylalanine, 3-amino-3-phenylpropionic acid, γ-aminobutyric acid, 3-amino-4,4-diphenylbutyric acid, tetrahydroisoquinoline-3-carboxylic acid, 4-aminomethylbenzoic acid, and aminoisobutyric acid,

AA^3 represents any amino acid,

AA^2 represents any amino acid, and

AA^1 represents any amino acid,

(3) a negatively charged stabilizing group selected from the group consisting of succinic acid, adipic acid, and glutaric acid, and

(4) optionally, a linker group not cleavable by TOP,

wherein the oligopeptide is directly linked to the stabilizing group at the amino terminus of the oligopeptide and the oligopeptide is directly linked to the therapeutic agent or indirectly linked through the linker group to the therapeutic agent at a second attachment site of the oligopeptide,

wherein the stabilizing group reduces acute toxicity of the compound when administered *in vivo*, and

wherein the compound is cleavable by TOP.